

Ethical Considerations in Community–Engaged Research in International Studies

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Disclaimer

Community engaged research

Framework for community involvement in:

- Research question
- Study design
- Recruitment and retention strategies
- Methods
- Data collection
- Interpretation
- Results dissemination

Community

- Group of people with common social ties, perspectives, and joint action in geographical locations or settings
- Not necessarily homogeneous and don't speak with one voice
- Risks and benefits of research affect not only individual participants but also the community

Potential consequences of lack of community engagement

- Failure to address complexity of health needs
- Failure to assess true impact of interventions
- Failure to initiate a project
- Failure to recruit and retain subjects
- Shutdown of entire research program



Suspensions mount against U.S. laboratory

Abdul Khalik, The Jakarta Post, Jakarta | Sat, 04/26/2008 12:02 PM

A | A | A |

The U.S. Namru-2 research lab has increasingly been accused of providing little benefit to Indonesia, with officials, lawmakers and experts voicing suspicion the lab is used for intelligence activities.

The criticism mounted following the United States' demand that Indonesia grant diplomatic status to all of its 19 citizens working at the Naval Medical Research Unit No. 2 (Namru-2) in Jakarta.

University of Indonesia international law professor Hikmahanto Juwana said diplomatic immunity given to the U.S. researchers violated international law.

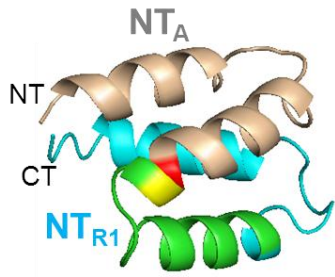
He cited the Vienna Convention that says only diplomats are entitled to immunity.

"We are wondering what the use of diplomatic immunity is for a researcher. Are they so in danger of being arrested or prosecuted in their work that they need protection?"

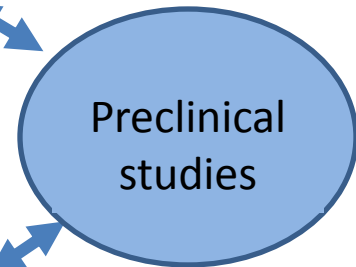
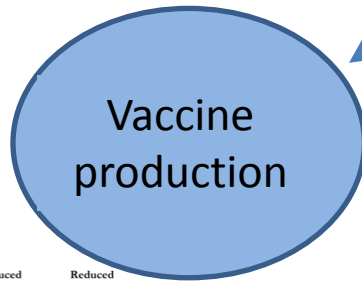
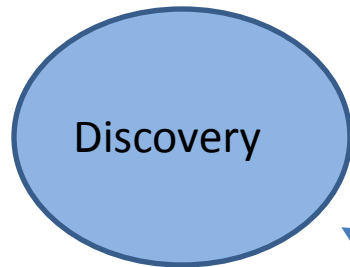
"Is Indonesia so weak that they can protect foreigners working here?" he told *The Jakarta Post* on Friday.

Laboratory of Malaria Immunology and Vaccinology

- Antigen & Biomarker discovery
- Immunopathogenesis
- Immunity

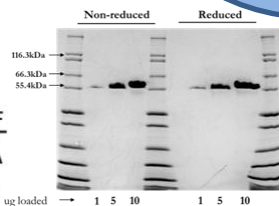


- Protein production
- Conjugation
- Formulation
- QA/QC



- Animal studies
- GLP tox

- Phase 1 & 2, US & Mali
- Proof of concept



Clinical Development of Malaria Vaccines

- First in human studies in malaria naïve adults (typically US, Europe, or Australia) to establish initial safety and immune responses (Phase 1a, Phase 2 if challenge component)
 - Immediately followed by studies in malaria exposed adults, usually in Africa (Phase 1b)
 - If safe and immunogenic age de-escalate to children and infants (Phase 1b and Phase 2)
 - Children are defined as vulnerable populations: must have likely benefit
- Risk is reduced by careful preclinical evaluation but not eliminated

Phase 1 Trial of Malaria Transmission Blocking Vaccine Candidates Pfs25 and Pvs25 Formulated with Montanide ISA 51

Yimin Wu^{1¶}, Ruth D. Ellis^{1¶}, Donna Shaffer², Erica Fontes², Elissa M. Malkin^{1¶a}, Siddhartha Mahanty^{1¶b}, Michael P. Fay³, David Narum¹, Kelly Rausch¹, Aaron P. Miles^{1¶c}, Joan Aebig¹, Andrew Orcutt¹, Olga Muratova¹, Guanhong Song¹, Lynn Lambert¹, Daming Zhu¹, Kazutoyo Miura¹, Carole Long^{1¶d}, Allan Saul^{1¶e}, Louis H. Miller¹, Anna P. Durbin^{2¶}

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RESEARCH

Open Access

Anaemia in a phase 2 study of a blood stage falciparum malaria vaccine

Ruth D Ellis^{1*}, Michael P Fay², Issaka Sagara³, Alassane Dicko³, Kazutoyo Miura¹, Merepen A Guindo³, Aldiouma Guindo³, Mahamadou S Sissoko³, Ogobara K Doumbo³, Dapa Diallo³

**"Cytokine Storm" in the Phase I Trial of
Monoclonal Antibody TGN1412: Better
Understanding the Causes to Improve PreClinical
Testing of Immunotherapeutics**

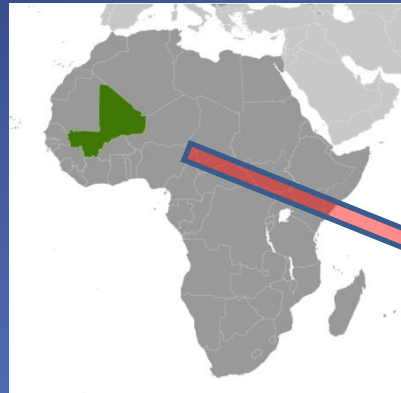
Richard Stebbings, Lucy Findlay, Cherry Edwards, David Eastwood, Chris Bird, David North, Yogesh Mistry, Paula Dilger, Emily Liefoghe, Isabelle Cludts, Bernard Fox, Gill Tarrant, Jane Robinson, Tony Meager, Carl Dolman, Susan J. Thorpe, Adrian Bristow, Meenu Wadhwa, Robin Thorpe and Stephen Poole

J Immunol 2007;179:3325-3331

LMIV Vaccine Research

- 10 Investigational New Drug (IND) applications initiated
 - 10 Phase 1 trials in malaria naïve adults (US, Australia)
 - Challenge study in malaria naïve adults (UK)
 - 3 Phase 1 trials in Malian adults
 - Phase 1,2 trial in 336 Malian children
 - 3 epidemiologic studies in Malian villages to provide baseline data to support clinical trials
- Malian studies are by far the most successful in terms of community engagement

Mali



- Landlocked, mostly desert
- 4th highest infant mortality rate
- 205th in life expectancy
- ~50% of population < 15 y/o
- One of the 25 poorest countries in the world
- Stable democracy
- Relatively high % of GDP spent on health (7%)
- 90% Muslim
- Traditional health providers play a large role

Malaria Research and Training Center, Bamako, Mali

- 20 year history of collaboration with NIAID
- International Center for Excellence in Research (ICER)
- Established teams of vector biologists, epidemiologists, parasitologists, immunologists, and clinical trialists
- Located at University of Bamako, under Faculty of Medicine, Pharmacy, and Odonto-Stomatology (FMPOS)
- Researchers come from the villages impacted by the diseases under study



Strong local collaborators: international leaders in setting malaria research agenda



PROFILE: OGOBARA DOUMBO

Mali Researcher Shows How To Reverse Brain Drain

Relying mainly on homegrown talent, Doumbo leads a network in Mali that does state-of-the-art studies of mosquito genetics, tracks drug resistance, and tests new vaccines

BAMAKO, MALI—On a bluff overlooking a flat Sahelian landscape, evening finds most offices empty at the University of Bamako's Faculty of Medicine. But a few lights remain on in the Malaria Research and Training Center (MRTC), and three Ph.D. candidates wait to speak with the director, Ogobara Doumbo. He leaves in a few days for Geneva to present new research affecting World Health Organization (WHO) guidelines on malaria prevention for children. But he makes space in the lab to discuss with a visitor what makes MRTC a paradox.

Doumbo, in his mid-50s but still looking like a student, smiles faintly when he speaks about his protégés, who recently led a roomful of top West African scientists through a comprehensive research discussion. Only in Mali, he says, will you find a critical mass of African Ph.D.s, with no loss to brain drain.

Bamako, a capital city of dusty streets on the banks of the Niger River, is not a place you expect to find a world center for research. Serving one of the world's poorest countries, Mali's health system is stretched to the breaking point. Yet on this bluff known



Traditionalist. A grandson of healers, Doumbo dreamed of becoming a village doctor.

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Regulatory Structure

- Protocols reviewed internally at NIAID for scientific validity
- Ethical review by both NIAID and University of Bamako/ FMPOS IRBs/ECs
- Reviewed by NIAID intramural regulatory group
- Reviewed by FDA and Mali Ministry of Health if investigational product
- Safety overseen by local medical monitor, NIAID Data Safety and Monitoring Board
- Study site monitored by NIAID for compliance with good clinical practice
- Study insurance required by FMPOS EC and Mali MOH
- Additional site monitoring by WHO

Dual Ethical Review of Protocols: Value Added

- NIAID IRB
 - Scientific elements
 - Assessment of risk/benefit
 - Regulatory issues (FDA requirements)
- FMPOS Ethics Committee
 - Community standards
 - Compensation
 - Family issues
 - Consent/assent
 - Benefit to community

Ethics review in Mali

- 3 ethics committees review human subjects research in Mali; FMPOS typically reviews more complex/risky studies. ~50 new submissions annually
- Staff: 2 part time support
- Protocols and consents translated into French prior to review (not Investigators Brochures)
- Strong support from NIH: ethics training for researchers and committee members conducted in collaboration with Department of Bioethics in 2003 and 2007
- (NIAID IRB: 32 initial reviews annually, 4 full time staff)

Study design/protocol development

- Vaccine trial objectives pre-defined (safety and immunogenicity), not much flexibility
 - Blood draws limited due to community sensitivity
 - Use of comparator vaccines (active, not placebo) in Mali increases benefit to participants
 - Standard of care, free medicines, follow up, and referrals
 - Frequent screening leads to earlier diagnosis and treatment, improved health outcomes
- Problem: research activities reduce frequency of outcomes of interest (malaria), more so if active intervention to find and treat malaria cases. **How to preserve data integrity and usefulness of field site while maintaining benefit to community?**

Community Permission for Medical Research in Developing Countries

Dapa A. Diallo,^{1,2} Ogobara K. Doumbo,^{1,2} Christopher V. Plowe,³ Thomas E. Wellems,⁴ Ezekiel J. Emanuel,⁵ and Samia A. Hurst⁵

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The realization of the need for community consent, or more accurately community permission, for research has occurred relatively recently. Practical experience with it is scarce. This article describes the Malian experience at a malaria vaccine study site. We describe a process that we used to obtain community permission. The process had 6 steps: (1) a study of the community, (2) an introductory meeting with leaders, (3) formal meetings with leaders, (4) personal visits with leaders, (5) meetings with traditional health practitioners, and (6) recognition that obtaining permission is a dynamic process. We discuss documentation of community permission for research and outline the reasons why the community-level process we used was practically necessary and ethically appropriate. Far from competing with the individual informed consent process, the process of obtaining community permission both initiated and facilitated the process of disclosure for individual informed consent.

Clinical Infectious Diseases 2005;41:255-9

- Study community and identify leaders
- Introductory meetings, formal and informal
- Meet with traditional health providers
- Obtain permission as part of a dynamic consultative process, including meetings to discuss important changes in study design

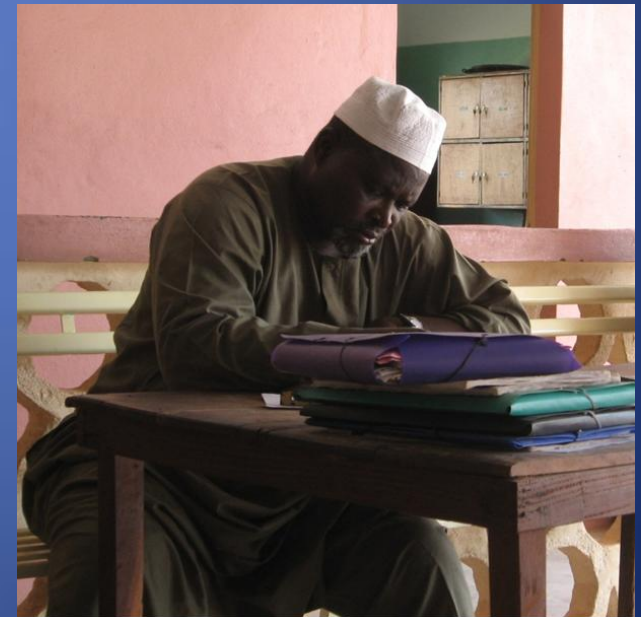


Recruitment and Retention

- Enhanced by getting early “buy in” and making community leaders part of the study team
- Announcement of study recruitment at community meeting
- Community as a whole understands benefits of research and importance of follow up in achieving study outcomes
- Problems with loss to follow up brought to community for help with solutions

Data Collection

- Principal and sub-investigators come from the community
- Sub-investigators often live in the village during the course of the study
- Local “guides” are responsible for facilitating community consent, recruitment, follow up reminders, clerical procedures, and in some cases conduct follow up visits



Benefits to community

- Presence of medical personnel in the village as part of research team
- Construction and/or renovation of clinics and health infrastructure (water, electricity)
- Provision of medications
- Referrals and transportation

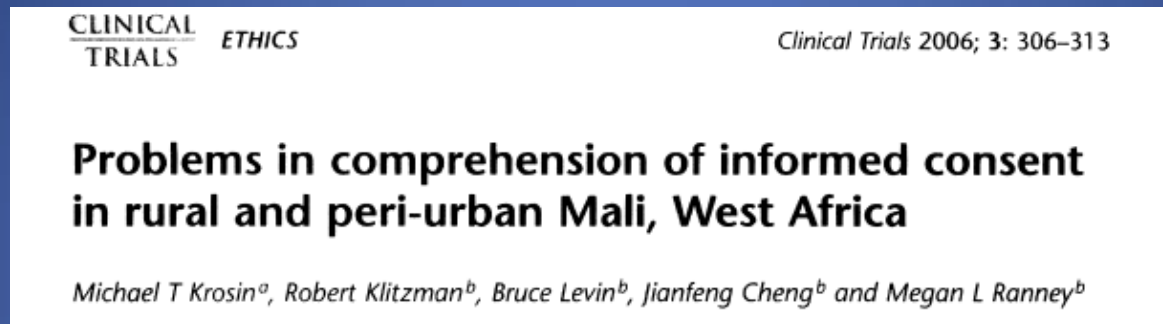


Individual consent: a basic principle of ethical research

Individual consent is complicated by:

- Language issues: consent written in English, translated to French, and administered in local language (which does not have a written form)
- Illiteracy and lack of basic scientific knowledge
- Gender issues
- Guardianship issues (who can give consent)

Some data suggests that research participants in developing countries are not likely to understand research and thus may often fail to provide valid informed consent:



- 90% of respondents did not understand withdrawal criteria
- 93% did not understand the existence of study side effects
- 74% did not understand that they were enrolled in an investigation as opposed to receiving therapy.

➤ But: comprehension is a problem in the developed world too.

Quality of informed consent in cancer clinical trials: a cross-sectional survey

Steven Joffe, E Francis Cook, Paul D Cleary, Jeffrey W Clark, Jane C Weeks

Lancet 2001; 358: 1772–77

Unique Data Set

- Early phase clinical trials of malaria vaccines conducted in US (Johns Hopkins University Center for Immunization Research, Washington DC), and Mali
- True/false questionnaires used to assess understanding of essential elements: risk, voluntariness, study procedures
- Incorrect answers were reviewed with study volunteers and all final answers correct before enrollment
- The same vaccines and similar trial designs were used in the US and Mali and questionnaires were very similar: opportunity to compare responses and understanding between populations

Comparing the Understanding of Subjects Receiving a Candidate Malaria Vaccine in the United States and Mali

Ruth D. Ellis, Issaka Sagara, Anna Durbin, Alassane Dicko, Donna Shaffer, Louis Miller, Mahamadoun H. Assadou, Mamady Kone, Beh Kamate, Ousmane Guindo, Michael P. Fay, Dapa A. Diallo, Ogobara K. Doumbo, Ezekiel J. Emanuel, and Joseph Millum*

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Am. J. Trop. Med. Hyg., 83(4), 2010, pp. 868-872

Results/Conclusions

Questionnaires were not intended for data collection and methods were not standardized, so interpret with caution!!

But...

- Participants at both sites well informed, with high scores overall
- Mali volunteers are less informed: errors in questionnaire administration, significant effect of location seen
- Women in Mali less informed vs men in US
- Older volunteers at both sites less informed

Concern about poor understanding relative to US does not appear to be supported

Interpretation and dissemination

- Local collaborators are primary/senior authors on publications
- Research results are communicated to villagers at meetings, which are a dialogue rather than one-way presentation of results
- Results of one study are connected to the next (community consent for next study)

Community engaged research in LMIV/MRTC collaborations

Framework for community involvement in:

- ✓ Research question
- ✓ Study design
- ✓ Recruitment and retention strategies
- ✓ Methods
- ✓ Data collection
- ✓ Interpretation
- ✓ Results dissemination



Weaknesses of the model

- Assumes that local collaborators represent the community
- Language and cultural barriers limit ability of outside collaborators to assess impact
- Women are under-represented as scientists and study team members, under-represented at community meetings
- External partners are reliant on local partners for interpretation and guidance regarding local conditions
- Lack of transparency

- Potential for conflict of interest
- Power imbalance (US > Mali, investigators > participants)
- Cost: more expensive to maintain relationships with community
- Time: takes longer to negotiate and build consensus
- High level of community commitment and benefit may put pressure on individuals to participate or not withdraw from research

Contrast with US/developed sites

	US/Developed	Mali
Resources	High	Low
Burden of disease	Low	High
Understanding of research	Fair/variable	Fair/may be reduced in some populations
Importance of research to community	Variable	High
Community input in study objectives and design	Minimal; community representatives on IRB	High, if assume that local collaborators represent community

	US/Developed	Mali
Community participation in research conduct	Low/variable	High
Research injury compensation	None in US (and often no health insurance)	Yes
Recruitment/retention	Fair/variable	High
Trust	Fair/variable	High
Results dissemination	Not required – typically by letter	Community meeting
Variables affecting outcomes	“research shopping”	High background rates of disease

How to replicate Malian success?

- Partner with strong local collaborators
- Provide long term financial and scientific support: reduces brain drain and promotes stable relationships between teams and community. Endangered in current budgetary climate
- Encourage commitment from local research institutions
- Cultivate culture of connectedness
- Avoid “drop in” projects
- Avoid “drop in” PIs
- Recruit team members from community, and provide opportunities for them to give input

When bad outcomes occur, the community will be better prepared and less likely to look for villains





Further Reading

- Immortal Life of Henrietta Lacks (Rebecca Skloot)
- Research Across Borders: Presidential Commission for the study of Bioethical Issues http://bioethics.gov/cms/sites/default/files/PCSBI-IRP_Research-Across-Borders.pdf
- Moral Science: Protecting Participants in Human Subjects Research <http://bioethics.gov/cms/sites/default/files/Moral%20Science.pdf>
- Practicing community engaged research <http://www.citiprogram.org/citidocuments/Duke%20Med/Practicing/community-engaged-research-4.pdf>
- Do IRBs Protect Human Research Participants? <http://jama.ama-assn.org/content/304/10/1122.full?etoc#AUTHINFO>

Acknowledgements

MRTC

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- Alassane Dicko
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- Mahamadoun H. Assadou
- Mamady Kone
- Beh Kamate
- Ousmane Guindo
- Merepen Agnes Guindo
- Dapa Diallo
- Ogobara Doumbo

JHU/CIR

- Anna Durbin
- Donna Shaffer

Study volunteers!



NIH Bioethics

- Joe Millum
- Ezekiel Emmanuel

NIAID Biostatistics

- Mike Fay
- Wenjuan (Jessie) Gu

NIAID DIR

- Joseph Shott

LMIV

- Yimin Wu
- Mark Pierce
- Louis Miller
- Regina White
- Alemush Imeru
- Patrick Duffy